DEATAILED ACTION

Status of the Claims

Claims 5, 50, 57-62 and 64-69 are pending in the instant application; claims 5, 58-60 and 64-69 are withdrawn; claims 50, 57, 61 and 62 are the subject of the Office Action below.

Information Disclosure Statement

The information disclosure statement IDS submitted on March 31, 2008, has been considered by the Examiner. The submission is partially compliant with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

However, reference citation no. 2, has not been considered since only three out of five total pages the document have been provided. This listing of this reference has been lined through.

Claim Rejections - 35 USC § 103 – Maintained

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. § 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 50 and 57 are obvious over Nienaber, Dauter and Wlodawer:

The rejection of claims 50 and 57, under 35 U.S.C. § 103(a) as being unpatentable over Nienaber *et al.*, *Nature Biotechnology 18*:1105-1108 (**2000**), in view of Dauter *et al.*, *Acta Crystallographica D57*:239-249 (**2001**), as evidenced by Wlodawer *et al.*, Nature Structural Biology 8(5):442-446, is maintained.

Applicants allege that the claimed invention is not rendered obvious in view of the cited references, and selectively mischaracterizes the references. Regarding the disclosure of Nienaber, Applicants suggest that because Nienaber purportedly concludes:

> "…that while this experiment gave an electron density map different from the native uncomplexed crystal, the identification of the ligand was not determined because of low resolution and "the mixture was not designed to be shape-diverse." Id. (emphasis added).
>
> Given the disclosure above, Nienaber would not have rendered obvious the instant claims, which require the step of combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine. Rather, Nienaber solely taught the use of mixtures that were shape-diverse and emphasized the importance of using diverse shapes."

Reply, page 6, lines 19-26.

Applicants further allege that Dauter does provide a basis for the rejection, and focus on Dauter's specific teachings directed towards the PCP enzyme, the teaching of the practical aspects of solving crystal structures, and discussion of phase problems:

> "Dauter does not cure the defects of Nienaber and does not render obvious, alone or in combination with Nienaber, methods for designing a lead candidate by combining a crystalline biological target molecule with a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine, as required by the instant claims. Rather, Dauter (i) teaches an elucidation of a crystal structure of an enzyme known as pepstatin-insensitive carboxyl proteinase (PCP) from Pseudomonas sp. 101; and (ii) discusses "the practical aspects of solving the crystal structure of PCP and analyze[s] both the successful experiments and the failed ones that utilized different crystal forms." Dauter et al., at 240 (emphasis added). Additionally, Dauter's purpose in solving the structure of PCP was to validate a solution to the phase problem for proteins with unknown folds. Id. at 239."

Reply, paragraph bridging pages 6 and 7.

Applicants also appear to be of the opinion that Wlodawer does not properly combine with the other reference in demonstrating how the claims are not patentable (Reply, paragraph bridging pages 7 and 8). Applicants then summarize the alleged impropriety of the rejection as follows:

> "Applicant respectfully submits that Examiner has not established that claim 50 is prima facie obvious in view of the references relied on by the Examiner because at least one limitation of claim 50, i.e., a mixture comprising at least two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine," is not taught or suggested by any of these references."

Reply, page 7, lines 20-24.

In response to Applicants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Instead, the combination clearly teaches each of the limitations for the reasons explained in the rejection below. Contrary to Applicants' summary of Dauter, Dauter does in fact teach the crystalline biological target, and mixture of two compounds wherein one of the compounds comprises bromine:

> "A very different crystal form (form III) was obtained from a sample consisting of a 1:1 complex of PCP [*i.e.*, the claimed biological target molecule] with modified tyrostatin in which the putative P3 tyrosine was replaced with a p-iodophenylalanine... [t]he bromine derivative was prepared by soaking the crystals for 30 s in a solution containing 1 M sodium bromide [*i.e.*, the claimed compound comprising bromine], 1.2 M lithium sulfate [*i.e.*, the other of the two compounds in the mixture], 14% glycerol in Tris buffer pH 7.5."

Dauter, page 241, col. 1. Considering that the improved protein structure elucidation by using bromine in multiwavelength anomalous diffraction as taught by Dauter is readily apparent, one of ordinary skill in the art would clearly appreciate the combination with the combinatorial approach of Dauter for screening a number of ligands-protein complexes using x-ray

crystallography for drug discovery. The art is clearly analogous, and the combination would readily be recognized as a structure-based discover process where the target crystal structure would server to identify putative inhibitors using a library of compounds, and would further guide the chemistry and development of lead compounds.

Therefore the rejection is maintained.

Reiterated Rejection:

Claim 50 is directed to a method for designing a lead candidate compound towards a biological target molecule comprising, combining the target with a mixture comprising two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties comprising bromine, followed by a structural determination, followed by the selection of "information" for the design of the lead candidate.

Nienaber teaches a method for screening a library of candidate compounds having binding affinity towards a given target biomolecule as a means towards developing a lead compound that has optimized binding properties. The method that Nienaber relies upon utilizes x-ray crystallography for making structural determinations, namely, by monitoring changes in the electron density of the biological target in the free and ligand-bound state (page 1105, col. 1, second paragraph). Nienaber exemplifies lead compound development using data from the binding of other ligands to the same target, and confirms it experimentally:

> "The primary screening data (structure) of compound 5 (Fig. 2A) bound to urokinase permitted a direct link to ***structure-directed lead optimization***. The structure reveals that the quinoline 8-position is directed toward a subsite termed the S1β pocket bounded by Gly 218, Ser 146, the Cys 191-Cys 220 disulfide bridge, the side chain of Lys 143, and part of Gln 19219 (Fig. 2B). In a previous study with the lead compound 2-naphthamidine, linking an amino-pyrimidyl group into this site was found to result in a substantial increase in binding potency (Ki = 5 μM to Ki = 0.03 μM, ref. 18, Fig. 2B), but the resultant compound exhibited no oral absorption. ***An overlay of the structures of the 8-aminopyrimidyl-2-naphthamidine and 8-hydroxy-2-aminoquinoline shows that although the directional vector from the 8-position of each molecule is different, the new lead can also access the S1β site (see Fig. 2B)***. To test this hypothesis, the ***8-aminopyrimidylsubstituted 2-aminoquinoline was synthesized*** and tested for inhibition as well as binding by crystallography. ***The optimized compound exhibited a 100-fold increase in inhibitory potency*** (Ki = 56

> μM to Ki = 0.37 μM, Fig. 2C) that was similar to the boost conferred in the naphthamidine series."

Nienaber, page 1106, col. 2, last paragraph (emphasis added).

Although Nienaber utilizes x-ray crystallographic methods for determining the structure of the ligand bound to the biomolecule, Nienaber does not explicitly teach that the crystal having the biomolecule and ligand also comprises a second compound having anomalous dispersion properties, as in step 'a' of claim 50.

Dauter teaches a method for determining the crystal structure of pepstatin-insensitive carboxyl proteinase (PCP), by soaking a PCP crystal, wherein the PCP is bound with tyrostatin, in the presence of sodium bromide and lithium sulfate (see page 241, column 1). The sodium bromide has anomalous dispersion properties, which are used in the measurement, and are used to determine the structure of the PCP-ligand complex (see page 244, col. 2, paragraph 3, and reference to structure Wlodawer, which is cited in this rejection as evidence of the PCP-ligand structure). As in claim 63, Dauter teaches the use of bromine.

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Nienaber, Dauter and Wlodawer, are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved x-ray technique and advances presented by Dauter, which are consistent for high-throughput screening, as in Nienaber for developing lead compounds based on the x-ray data obtained by screening a library of compound having binding affinity to a given biomolecule (see last sentence of Abstract in Dauter). Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Claims 50, 57, 61 and 62 are obvious over Nienaber, Dauter, Wlodawer and Reddy:

The rejection of claims 50, 57, 61 and 62, under 35 U.S.C. § 103(a) as being unpatentable over Nienaber *et al.*, *Nature Biotechnology 18*:1105-1108 (**2000**), in view of Dauter *et al.*, *Acta Crystallographica D57*:239-249 (**2001**), as evidenced by Wlodawer *et al.*, Nature Structural Biology 8(5):442-446, and in view of Reddy *et al.*, JACS 123:6246-6252 (**2001**).

Applicants traverse the rejection for the same reasons as presented above. Applicants further contend that Reddy does not address alleged absent teaching of any of Nienaber, Dauter or Wlodawer.

Applicants arguments have been considered in full, however, are not found persuasive for at least the reasons presented above.

Reiterated Rejection:

Claim 50 is directed to a method for designing a lead candidate compound towards a biological target molecule comprising, combining the target with a mixture comprising two compounds, wherein at least one of the compounds comprises a substituent having anomalous dispersion properties, followed by a structural determination, followed by the selection of "information" for the design of the lead candidate.

Nienaber teaches a method for screening a library of candidate compounds having binding affinity towards a given target biomolecule as a means towards developing a lead compound that has optimized binding properties. The method that Nienaber relies upon utilizes x-ray crystallography for making structural determinations, namely, by monitoring changes in the electron density of the biological target in the free and ligand-bound state (page 1105, col. 1, second paragraph). Nienaber exemplifies lead compound development using data from the binding of other ligands to the same target, and confirms it experimentally:

> "The primary screening data (structure) of compound 5 (Fig. 2A) bound to urokinase permitted a direct link to ***structure-directed lead optimization***. The structure reveals that the quinoline 8-position is directed toward a subsite termed the S1β pocket bounded by Gly 218, Ser 146, the Cys 191-Cys 220 disulfide bridge, the side chain of Lys 143, and part of Gln 19219 (Fig. 2B). In a previous study with the lead compound 2-naphthamidine, linking an amino-pyrimidyl group into this site was found to result in a substantial increase in binding potency (Ki = 5 μM to Ki = 0.03 μM, ref. 18, Fig. 2B), but the resultant compound exhibited no oral absorption. ***An overlay of the structures of the 8-aminopyrimidyl-2-naphthamidine and 8-hydroxy-2-aminoquinoline shows that although the directional vector from the 8-position of each molecule is different, the new lead can also access the S1β site (see Fig. 2B)***. To test this hypothesis, the ***8-aminopyrimidylsubstituted 2-aminoquinoline was synthesized*** and tested for inhibition as well as binding by crystallography. ***The optimized compound exhibited a 100-fold increase in inhibitory potency*** (Ki = 56

> μM to Ki = 0.37 μM, Fig. 2C) that was similar to the boost conferred in the naphthamidine series."

Nienaber, page 1106, col. 2, last paragraph (emphasis added).

Although Nienaber utilizes x-ray crystallographic methods for determining the structure of the ligand bound to the biomolecule, Nienaber does not explicitly teach that the crystal having the biomolecule and ligand also comprises a second compound having anomalous dispersion properties, as in step 'a' of claim 50.

Dauter teaches a method for determining the crystal structure of pepstatin-insensitive carboxyl proteinase (PCP), by soaking a PCP crystal, wherein the PCP is bound with tyrostatin, in the presence of sodium bromide and lithium sulfate (see page 241, column 1). The sodium bromide has anomalous dispersion properties, which are used in the measurement, and are used to determine the structure of the PCP-ligand complex (see page 244, col. 2, paragraph 3, and reference to structure Wlodawer, which is cited in this rejection as evidence of the PCP-ligand structure). As in claim 63, Dauter teaches the use of bromine.

As in claims 61 and 62, Reddy teaches an iterative, computer-assisted, drug design strategy that combines molecular design, molecular mechanics, molecular dynamics (MD), and free energy perturbation (FEP) calculations with compound synthesis, biochemical testing of inhibitors, and crystallographic structure determination of protein-inhibitor complexes was successfully used to predict the rank order of a series of nucleoside monophosphate analogues as fructose 1,6-bisphosphatase (FBPase) inhibitors (see Figure 1, and description thereof; see Figure 3, and description thereof).

One of ordinary skill in the art would have had a reasonable expectation of success in arriving at the invention as claimed because each of Nienaber, Dauter and Wlodawer, are directed to the use of x-ray crystallography for structural analysis of protein-substrate interactions. One of ordinary skill in the art would have been motivated to utilize the improved x-ray technique and advances presented by Dauter, which are consistent for high-throughput screening, as in Nienaber for developing lead compounds based on the x-ray data obtained by screening a library of compound having binding affinity to a given biomolecule (see last sentence of Abstract in Dauter). Therefore the invention as whole was *prima facie* obvious at the time it was invented.

The further modification of the method of Nienaber and Dauter by Reddy would be a recognized advantage because of the accelerated pace and experimental confidence that established molecular dynamics simulations provide in lead compound development. Therefore the invention as whole was *prima facie* obvious at the time it was invented.

Conclusions

No claim is allowable.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

If Applicants should amendment the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (*e.g.*, if the amendment is not supported *in ipsis verbis*, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Jeff Lundgren whose telephone number is 571-272-5541. The Examiner can normally be reached from 7:00 AM to 5:30 PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James (Doug) Schultz, can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JSL

/JD Schultz, PhD/

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